Medical Staff Conference

Therapeutic Dilemmas in Type II Diabetes Mellitus—Improving and Maintaining β-Cell and Insulin Sensitivity

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *The dietary and drug therapy for non-insulin-dependent diabetes mellitus seems to be a constant source of controversy, possibly because we seem to have made more progress in learning about the risks and complications of different treatments than in learning about the pathogenesis of the condition. What we have learned about treatment and pathogenesis is nonetheless fascinating, and we are fortunate to have John Karam, MD, Professor of Medicine and Associate Director of the Metabolic Research Unit, here to discuss the therapeutic dilemmas posed by type II diabetes mellitus.*

JOHN H. KARAM, MD†: Non-insulin-dependent diabetes mellitus (NIDDM), or type II diabetes, affects more than 8 million people in the United States and accounts for morbidity and mortality from vascular complications with twice the risk as for age- and sex-matched nondiabetic populations.[1] Unfortunately, the pathogenesis of hyperglycemia in this disorder remains obscure, and perhaps for this reason many questions remain unanswered regarding the advantages and disadvantages between sulfonylurea or insulin treatment in patients with NIDDM. In addition, recent reports documenting the susceptibility of the pancreatic β-cell to becoming desensitized to glucose[2-5] and to develop tachyphylaxis to sulfonylureas in vivo[6] have raised further questions as to the manner in which these pharmacologic agents should be administered to be maximally effective. In this presentation, I will review current concepts concerning the pathogenesis of hyperglycemia in patients with type II diabetes, the effect of obesity in this population, and the use of diet, exercise, sulfonylureas, and insulin in the treatment of this disorder, with a caveat that "desensitization" unfortunately seems to occur with all four of these therapeutic modalities.

Pathogenesis of Hyperglycemia in NIDDM and Its Effects on Insulin Secretion and Action

All investigators generally agree that in patients with NIDDM who have fasting hyperglycemia, there are at least two major defects that contribute to the hyperglycemia: a defective pancreatic β-cell response to glucose[7,8] and an impaired action of insulin on its target tissues.[8,9] Because either one of these defects can secondarily induce as well as aggravate the other defect, considerable speculation has arisen as to whether only one of them is a primary defect or whether they coexist initially in the pathogenesis of NIDDM. Regardless of which defect is the primary one, it has become well established that correcting the hyperglycemia by any means, including diet, sulfonylureas or insulin therapy, can improve the pancreatic β-cell response to glucose[10,11] and the impaired tissue response to insulin.[11] This amelioration of both defects by any of these therapeutic maneuvers has given support to the concept that hyperglycemia itself can directly desensitize the pancreatic β-cell[3,4] and that it can in some way induce peripheral tissue resistance as well.[12] This latter observation has stimulated a reevaluation of traditional concepts that sulfonylurea drugs have a peripheral effect of potentiating insulin action because any glucose-lowering effect from increasing insulin secretion in patients with NIDDM would thereby lower peripheral resistance and enhance insulin action.[13] Evidence that insulin therapy is just as effective as sulfonylurea therapy in reducing peripheral insulin resistance in NIDDM[14] and that sulfonylureas apparently have no therapeutic benefit in patients with type I diabetes in lowering insulin requirements or hyperglycemia[15] further supports the concept that the beneficial effects of sulfonylureas in patients with type II diabetes can be explained by their stimulation of pancreatic β-cells to provide more circulating insulin and thereby reduce hyperglycemia. This improved metabolic control can increase the effect of insulin on its target tissues without the need to invoke a direct effect of sulfonylureas on insulin action in vivo.

Role of Obesity in NIDDM

In most western societies, patients with NIDDM have a high prevalence of associated obesity. When this increased adipose mass is predominantly distributed in the truncal region and particularly within visceral mesenteries and omentum,[16] there is increased resistance to the action of insulin, particularly in hepatocytes. An intriguing hypothesis is based on data showing that an increased flux of fatty acids directed into the portal vein from excessive omental fat may be responsible for this hepatic insulin insensitivity.[16,17]

While a genetic predisposition to obesity has long been postulated in humans, only recently has substantial evidence been provided. Stunkard and co-workers have documented a

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ABBREVIATIONS USED IN TEXT
IGF-II = insulinlike growth factor II
NIDDM = non-insulin-dependent diabetes mellitus
UCSF = University of California, San Francisco

correlation between the weights of 540 adoptees and their biologic parents, but no correlation was evidenced with adopted parents.[18] Moreover, among identical twins, the concordance for obesity was twice as high as in dizygotic twins.[19] Yet it has been well established that providing a wide variety and an abundance of high-caloric "cafeteria food" can induce obesity in rats,[20] suggesting that acquired obesity can readily occur in affluent societies without requiring a specific genetic predisposition. Recent data on a newly discovered protein secreted into the blood of rodents from adipocytes and named "adipsin"[21] indicate that its levels are increased during food deprivation and reduced after glucose infusion. Of interest is its low level in models of genetic obesity such as "obob" and "dbdb" mice and "fafa" rats, but normal levels in an acquired-obesity model, the cafeteria-fed rat. This raises the question as to whether a reduced circulating level of adipsin in a human population could be a marker for a genetic type of obesity in contrast to acquired forms of obesity resulting primarily from ingesting high-calorie foods. Results of future surveys in this area will be of interest particularly because of possible therapeutic implications in genetic models of human obesity in which the absence of circulating adipsin could contribute to a reduced fat mobilization.

The Insulin Receptor and 'Postreceptor' Actions of Insulin

Recent characterization of the insulin receptor as possessing a tyrosine kinase within its β-subunit[22] has not only suggested ways for insulin to exert its effects but also indicates a number of possible defects to account for the postreceptor resistance to insulin in patients with type II diabetes.

The insulin receptor is composed of two pairs of distinct subunits derived from a single protein precursor molecule, and each subunit has a specialized function.[22] The α-subunit has a molecular weight of 130,000 daltons and is the portion of the receptor protruding from the cell surface that binds circulating insulin. The β-subunit is smaller with a molecular weight of 90,000 daltons, lies predominantly inside the cell, and contains an insulin-sensitive protein kinase. Each functioning insulin receptor is composed of two α- and two β-subunits. When insulin binds to the α-subunit, the β-subunit enzyme becomes activated, resulting in the phosphorylation of at least one of its own tyrosine components. This somehow results in the internalization of the insulin-insulin receptor complex. Czech has proposed a model in which this internalized complex promotes a cascade of phosphorylations from its activated kinase region that induces an intracellular compartment of proteins to move to the cell surface.[23] These include the glucose transporter protein, transferrin, the low-density-lipoprotein receptor and the insulinlike growth factor-II (IGF-II) receptor. Movement of these proteins—which are sequestered intracellularly during the postabsorptive period—to the cell surface during feeding can explain the actions of insulin on the transport of glucose and other nutrients in insulin target tissues and in promoting growth by giving circulating IGF-II access to a cell surface receptor.

On the basis of this model, a number of genetic defects distal to the insulin receptor might be postulated to account for "postreceptor" insulin resistance—such as abnormalities of the enzymes responsible for phosphorylation of the glucose transporter protein or a mutation of the glucose transporter itself or in its processing. Moreover, abnormalities of phosphatase enzymes might account for a delay in the normal restoration of the insulin receptor to its surface membrane locus, resulting in more resistance in some patients with NIDDM to the action of insulin.

Controversies Regarding Therapeutic Options in NIDDM

Diet and Exercise

In December 1986, a consensus development conference was convened at the National Institutes of Health to arrive at recommendations for the dietary management of patients with non-insulin-dependent diabetes mellitus.[24,25]

Considerable controversy was apparent regarding the content of such a diet. Some nutritionists expressed a concern that each of the three main foodstuffs—fat, protein, and carbohydrate—could be incriminated as contributing to the vascular complications of diabetes. Thus, when saturated fat intake is reduced as a prudent means of reducing the risk of macrovascular disease, questions arise as to the feasibility of replacing it with either protein or carbohydrate foods.

Brenner and Zatz and associates have suggested that a high-protein content in the diet can be harmful to kidneys and retinas by promoting increased hemodynamic effects on their microvasculature.[26,27] They report that vasodilatory effects of amino acids promote an increased blood flow of retinal vessels and hyperfiltration of renal glomeruli, thereby increasing permeability to macromolecules that contributes to basement membrane thickening and capillary damage.

Reaven, quoted by Kolata,[25] cautioned against replacing fat calories with carbohydrate in the diet because of certain potentially deleterious consequences such as an increase in circulating levels of insulin and triglycerides. He cited an association of hyperinsulinism with an increased risk of heart disease. This could be due to a correlation between hyperinsulinemia and an increase in various risk factors such as hypertension, increased very-low-density-lipoprotein levels, and reduced high-density-lipoprotein levels. Those comments prompted the chair of the planning committee for the consensus conference to note[25] that nutritionists have been placed in a bind when giving diet advice to patients with type II diabetes by the concern that a high-fat diet is bad for the heart, a high-protein diet is bad for the kidneys, and a high-carbohydrate diet may adversely increase cardiovascular risk factors.

Other areas of controversy relating to the content of the diet and addressed by the conference included whether certain carbohydrates such as those in beans or pasta induced less hyperglycemia—that is, have a lower "glycemic index"—than did other complex carbohydrates such as those in potatoes or bread, and, finally, whether purified fiber supplements were beneficial in controlling excursions of blood glucose or reducing hypercholesterolemia.

Dietary Recommendations of the Consensus Conference

The planning committee of the consensus conference admitted that further experimental data are needed before the

controversies about the content of the diet can be resolved. Until more evidence is available, however, they proposed the guidelines shown in Table 1 for the dietary treatment of patients with NIDDM.

The conference reaffirmed the need to restrict dietary fat to less than 30% of total calories, with saturated fat making up less than 10% of the total calories. Carbohydrate diets—up to 50% to 60% of total calories—may include sucrose as a taste additive in mixed meals of patients who are lean and do not have carbohydrate-induced hyperlipidemia as long as the sucrose content is less than 5% of carbohydrate calories. The panel did not recommend calculating specific glycemic indices in the dietary treatment of patients with NIDDM and saw no need to change the standard recommendation that proteins comprise 12% to 20% of the calorie content of the diet in people with normal renal function. They noted that studies claiming that dietary fiber was effective in lessening hyperglycemia and hypercholesterolemia were inconclusive. Furthermore, because high-fiber diets may be less palatable, require substantial changes in traditional food patterns, have effects on other nutrients, and can induce abdominal discomfort, particularly in diabetic patients with gastrointestinal neuropathies, they concluded that it was not advisable to use purified fiber supplements for diabetic therapy.[24] If persons wished to increase the fiber content of their diet, however, the panel felt that food high in soluble fiber might be used to replace some other carbohydrates.

Exercise Recommendations of the Consensus Conference

The panel reviewed recent data that seemed to contradict many commonly held beliefs about exercise as an adjunct to low-calorie diets in achieving weight reduction (Table 1). One study showed that the weight loss and improved glycemic control after 12 weeks of a low-calorie outpatient diet alone was not significantly augmented when a program of supervised exercise was added to the same diet in a matched group of NIDDM patients.[28] The authors surmised that obese patients frequently compensate after supervised exercise while dieting by either eating more, or moving less for the rest of the day—or both. Other studies reviewed by the consensus panel confirmed that when obese people entered an exercise program, they moved less during the remainder of the day, thereby canceling out the extra calories they expended while exercising.[25]

The consensus conference reaffirmed that weight maintenance is the cornerstone of diabetes therapy and advised overweight persons to lose weight and those not yet overweight to avoid becoming obese. The panel recommended moderate exercise as an adjunct to calorie restriction but could justify it more for its effect in preventing heart disease than for its aid in losing weight or reducing blood glucose levels.

Sulfonylurea Therapy

In patients with type II diabetes and chronic hyperglycemia, the pancreatic β-cells lose their initial incremental insulin responses to glucose but generally respond briskly to other β-cell secretagogues.[2,8] We have previously reported that this may not be a defect specific for glucose as seven patients with NIDDM were shown to lose their pancreatic β-cell responses to infusions of tolbutamide when they had sustained therapeutic blood concentrations of a first-generation sulfonylurea, tolazamide,[6] but retained responsiveness to an alternate β-cell secretagogue, glucagon. This state of refractoriness to intravenous tolbutamide stimulation was readily reversed when the sulfonylurea therapy was discontinued and β-cells once again responded to acute stimulation with tolbutamide.[6] An illustrative case of a patient manifesting this phenomenon of tachyphylaxis is described below, and data are shown in Figure 1.

The patient, a 56-year-old obese woman with non-insulin-dependent diabetes mellitus, had progressive hyperglycemia over a course of 20 years. She initially at age 39 did not have diabetes but had exaggerated insulin responses to glucose, attributed to her obesity. After diabetes developed, her pancreatic β-cells became less responsive to glucose but still responded briskly to other secretagogues such as glucagon, arginine, or tolbutamide and to combinations of these secretagogues.

As shown in Figure 1, her loss of an immediate insulin response to tolbutamide given intravenously during three intervals of long-term sulfonylurea therapy with tolazamide, but not during four corresponding intervals of diet therapy only, had relevant implications to the concept of tachyphylaxis, particularly because abrupt insulin release to the intravenous administration of glucagon persisted during long-term sulfonylurea therapy in this patient. Similar findings were observed in seven patients studied while receiving oral sulfonylurea therapy sustained for four weeks or longer (Figure 2). In these patients, whose cases were reported previously,[6] mean peak insulin increments five or ten minutes

TABLE 1.—*National Institutes of Health Consensus Panel Recommendations on Diet and Exercise in Non-Insulin-Dependent Diabetes Mellitus (NIDDM)*

Caloric restriction*	
500-1,000 kcal below daily requirements to promote gradual weight loss	
Nutrient content of diet	
Total fat intake	<30% of total calories
Saturated fat	<10% of total calories
Cholesterol intake	<300 mg per day
Protein intake	12%-20% of total calories†
Carbohydrate intake	50%-60% of total calories‡
Sucrose	Up to 5% of carbohydrate calorie intake in mixed meals
Glycemic indices	Not recommended at this time
Fiber intake	Foods high in soluble fiber may be used to replace other carbohydrates; purified fiber supplements are not recommended
Vitamins and minerals	Diet should be nutritionally complete and satisfy recommended dietary allowances
Exercise	
Effect of exercise on metabolic control in NIDDM is often variable and of small magnitude	
Exercise alone is ineffective for weight reduction unless accompanied by an appropriate diet	
Diet alone may be as effective for weight reduction as diet plus exercise in outpatients	
Exercise appears to have special benefits in reducing coronary heart disease in the general population	
Hazards of certain exercises are greater in patients with diabetes who have insensitive feet or proliferative retinopathy	

*Recommendations for obese patients.
†Patients with renal failure may need less protein.
‡Refers to patients without hypertriglyceridemia.

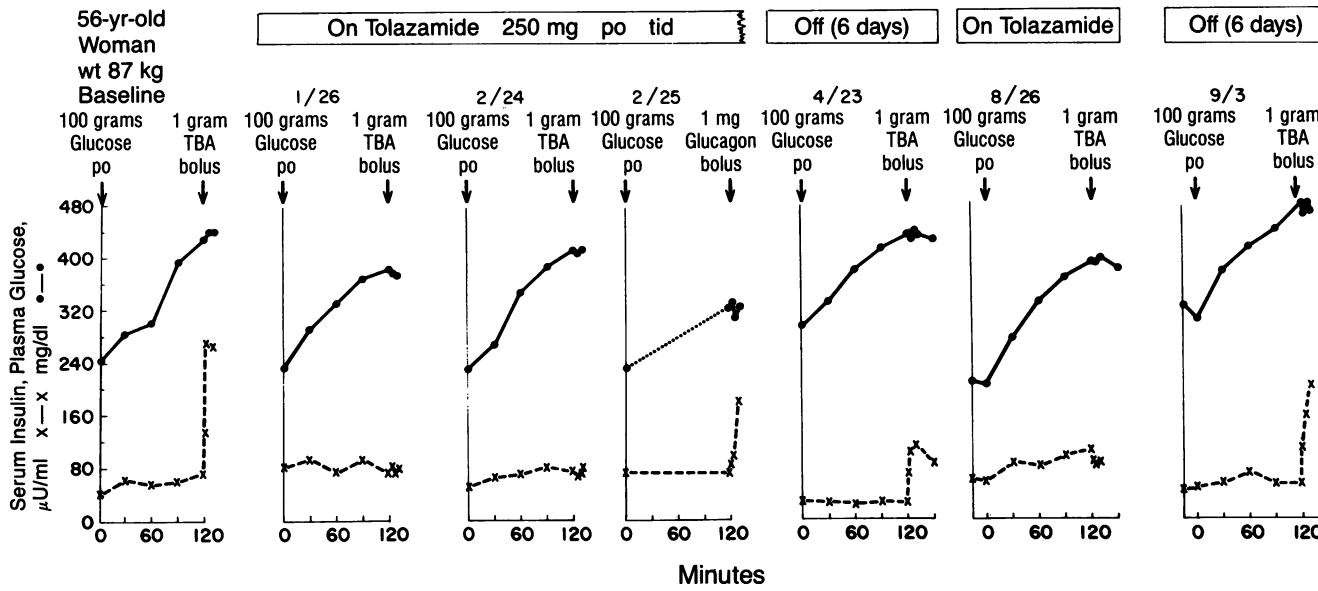

Figure 1.—The graphs show serial pancreatic β-cell stimulation testing with 1 gram tolbutamide (TBA) or 1 mg glucagon given intravenously 2 hours after 100 grams glucose were taken by mouth (po) in an obese woman with non-insulin-dependent diabetes mellitus while she is on or off long-term sulfonylurea therapy (from Karam et al,[6] with permission from the American Diabetes Association, Inc).

after tolazamide was given intravenously were 54 ± 11 μU per ml when not receiving tolazamide but were 0.14 ± 1.3 μU per ml during tolazamide therapy ($P < .001$), even though the serum insulin level rose rapidly after the intravenous administration of glucagon. These results suggest that different signal recognition systems exist on the pancreatic β-cell for various secretagogues such as glucose, tolbutamide, and glucagon, as shown in Figure 3. When exposed to sustained stimulation from chronic hyperglycemia as in NIDDM, the β-cell loses its ability to respond to an abrupt glucose load but retains its responsiveness to intravenous tolbutamide or glucagon. As a sustained level of sulfonylurea stimulation is achieved, the β-cell becomes desensitized to this agent and to glucose but retains its response to an intravenous bolus of glucagon.

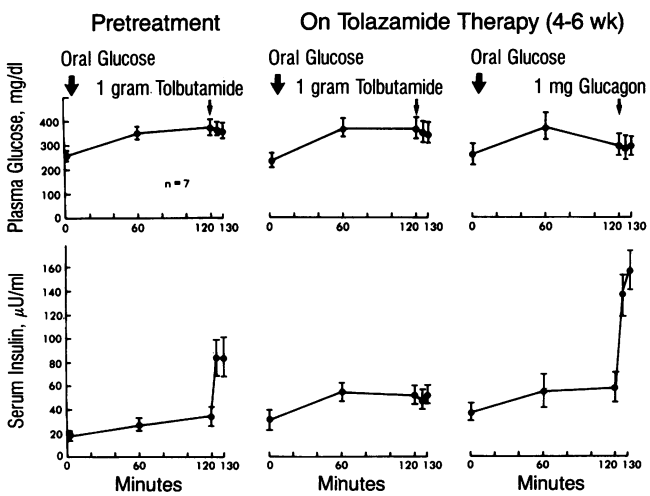

Figure 2.—The graphs show pancreatic β-cell stimulation with 1 gram tolbutamide (n = 7) or 1 mg glucagon (n = 6) given intravenously 2 hours after 50 to 100 grams oral glucose in 7 obese patients with non-insulin-dependent diabetes mellitus while off or on long-term sulfonylurea therapy. Results are expressed as means ± standard error of the mean (from Karam et al,[6] with permission from the American Diabetes Association, Inc).

These findings suggest that a state of tachyphylaxis or desensitization can develop in pancreatic β-cells during their exposure to sustained elevated concentrations of sulfonylureas, and once these sustained concentrations are reduced, the β-cells regain their sensitivity. These data suggest another possible contributing factor to explain the frequency of "secondary failure" to sulfonylurea therapy in NIDDM and suggest greater therapeutic effectiveness if these drugs were administered either intermittently or in "pulse" fashion using sulfonylureas with the shortest duration of action.

Insulin Therapy

More than 40 different pharmaceutic formulations of insulin are available in the United States, differing in concentrations, production method, molecular species, and in the adjuvant used to delay absorption so that action can be prolonged. Because patients with non-insulin-dependent diabetes mellitus are less sensitive to insulin than normal, it seems prudent to prescribe the least immunogenic insulins, such as human insulin, to lessen the induction of additional

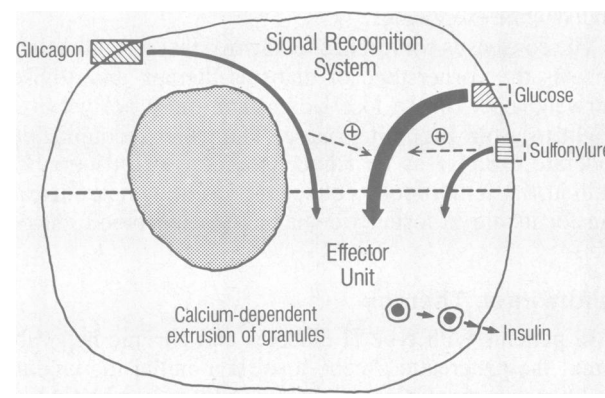

Figure 3.—The schematic diagram of the pancreatic β-cell depicts a model that has distinct signal recognition systems for different insulin secretagogues, which converge on a common pathway by which they discharge insulin.

TABLE 2.—*Available Human Insulin Formulations*

Type of Insulin	*Eli Lilly*	*Squibb-Novo*	*Nordisk-USA*
Regular, crystalline zinc	Humulin R	Novolin R	Velosulin Human
Isophane (NPH) insulin suspension	Humulin N	Novolin N	Insulatard NPH Human
Insulin zinc suspension (lente)	Humulin L	Novolin L	...
Extended insulin zinc suspension (ultralente)	Humulin U	...	...
70% NPH/30% regular	...	Novolin 70:30	Mixtard Human

insulin antagonism in the form of circulating anti-insulin antibodies. Unfortunately, even when pure human insulin is administered from the start of therapy, many patients will acquire some insulin antibodies, presumably because of polymerization of the human insulin at therapeutic dose levels. Human insulin is prepared by either recombinant DNA methods (Humulin [Eli Lilly & Co]) or enzymatic amino acid transpeptidation of pork insulin (Novolin [Squibb-Novo, Inc] or human insulin [Nordisk-USA]). Formulations of human insulin currently available in the United States are shown in Table 2.

Attempts to achieve near-normal glucose levels in obese patients with NIDDM by intensive insulin therapy can result in considerable weight gain. After 36 months of insulin therapy with an implantable pump that maintained normal glycohemoglobins, two obese patients with NIDDM gained 7.5 and 11.2 kg (16 and 25 lb), respectively.[29]

Because both β-cell function and sensitivity to insulin improve after intensive insulin therapy for patients with NIDDM,[11] a decrease in their insulin requirements should be expected as glycohemoglobins become normal.

Conventional insulin therapy using mixtures of regular and intermediate-acting insulin given twice a day is often prescribed. In contrast to lente insulin, NPH insulin does not seem to affect the rapid action profile of admixed regular insulin in vivo,[30] and it is therefore preferred over lente insulin when mixtures are prescribed.

Continually elevated insulin concentrations are known to "down regulate" the insulin receptors,[31] thereby attenuating insulin responsiveness analogous to the way chronic hyperglycemia desensitizes glucose disposal mechanisms[12] in a reversible manner.[11,14] Thus, it may be more effective to lessen hyperinsulinemia by administering insulin in a pulse-like manner using intermittent regular insulin doses, rather than relying primarily on large doses of intermediate-acting insulins. Moreover, insulin administered by nasal spray, if proved safe over the long run, could be of particular benefit in this regard because of the rapid onset but short duration of its biologic action.[32]

Combinations of Insulin and Sulfonylurea Therapy

The possible benefits of prescribing both insulin and sulfonylureas continue to be investigated in clinical trials. A recent review by Genuth of 17 published reports describing combined drug therapy of this type led him to the conclusions given in Table 3.[15] At present there does not seem to be any experimental basis for adding insulin to a regimen of sulfonylureas when the latter drugs are not effective. When this is the case, the use of sulfonylureas should be discontinued and only insulin prescribed. Conversely, when insulin therapy appears to be inadequate, particularly after large doses are being administered, it has been observed that adding sulfonylureas can improve glycemic control.[15]

TABLE 3.—*Combined Insulin and Sulfonylurea Therapy**

- Contraindicated in insulin-dependent diabetes mellitus
- Only modest glycemic improvement in trials of non-insulin-dependent diabetes mellitus (NIDDM), n=11
- No proven long-term advantage in NIDDM
- Current recommendations
  - Add sulfonylureas to therapy regimen of patients with NIDDM who respond poorly to high doses of insulin (>100 U/d)
  - Insulin alone is preferable to combination therapy in patients with NIDDM with failure due to sulfonylureas

*Modified from Genuth.[15]

Therapeutic Perspective

The optimal therapy for type II diabetes mellitus remains elusive in most of these patients for a number of reasons. Foremost is the high prevalence of obesity, which enhances insulin resistance in patients with NIDDM and which, in our affluent society, is so refractory to conventional attempts at weight reduction. In addition, until specific genetic markers for NIDDM become available, the confused heterogeneity of this disorder remains difficult to clarify, thereby hindering the selection of appropriate therapies for particular subgroups. Finally, the well-established pharmacologic concept of tachyphylaxis has recently been reemphasized because of the molecular biologic attempts to define its as-yet-obscure mechanism.[33] Tachyphylaxis and its related concepts of "desensitization," "tolerance," or "down regulation" raise the concern that current conventional regimens of glycemic therapy that provide sustained high concentrations of sulfonylureas or insulin over prolonged periods may reduce the therapeutic effectiveness of these agents. Future clinical trials using "pulse" therapy with shorter-acting sulfonylureas or insulin should help resolve this question. Moreover, resensitizing patients with NIDDM to comply with healthful diet and exercise patterns as well as restoring sensitivity to sulfonylureas or insulin would seem an appropriate goal in the treatment of these hyperglycemic patients with their desensitized pancreatic β-cells, "down-regulated" insulin receptors, and desensitized tissue responsiveness to insulin.

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